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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/523,809	03/13/2000	Michael P. Murphy	OGA-01002	6553

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EXAMINER	
KAUSHAL, SUMESH	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/523,809	MURPHY ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/ are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 10/31/07 has been acknowledged and fully considered. The applicant fails to file any *"Third Faria Declaration"* to which the applicant's remarks (dated10/31/07) are exclusively limited to.

Claims 31-71 are pending and are examined in this office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is ***571-273-8300.***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/31/07 has been entered.

Claim Rejections - 35 USC § 112

Claims 31-71 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the same reasons of record as set forth in the office action mailed on 03/15/07.

Nature of Invention:

Invention relates to an artificial skin construct.

Breadth of Claims and Guidance Provided in the Specification

The scope of instant claims encompasses a cultured skin construct having at least two layers, comprising: a) a first layer of cultured dermal fibroblast cells which produce a layer of extracellular matrix in the absence of exogenous matrix components during the culturing conditions *(any and all: growth factor and culture conditions not defined i.e. the support on which the cell are cultured)*; and (b) a second layer of keratinocyte cells disposed on the first layer to form an epidermal cell layer, wherein the epidermal cell layer is multilayered, stratified, differentiated and exhibits a basal layer, suprabasal layer, a granular layer and a stratum corneum; and wherein the bilayered cultured skin construct has a basement membrane present at the junction of the first and second layers (*wherein the keratinocyte cells makes an epidermal layer (as claimed) under any and all culture conditions: i.e. growth factors and culture conditions).*

The scope of instant claims encompasses further encompasses a cultured skin construct having at least two layers, comprising: a) a first layer of cultured dermal fibroblast cells which produce a layer of extracellular matrix in the absence of exogenous matrix components during the culturing conditions *(any and all: growth factor and culture conditions not defined, i.e. the support on which the cell are cultured)*; and (b) a second layer of keratinocyte cells disposed on the first layer to form an epidermal cell layer *wherein the keratinocyte cells makes an epidermal layer (as claimed) under any and all culture conditions: i.e. growth factors and culture conditions).*

The scope of invention further encompasses a cultured skin construct having at least three layers, comprising: a) a first layer of cultured dermal fibroblast cells which produce a layer of extracellular matrix in the absence of exogenous matrix components during the culturing conditions *(any and all: growth factor and culture conditions not defined)*; and b) a second layer of keratinocyte cells disposed on the first layer to form an epidermal cell layer (*wherein the keratinocyte cells makes an epidermal layer (as claimed) under any and all culture conditions: i.e. growth factors and culture conditions)*

c) and a third layer of cells deposed on the second layer. In addition the scope of invention as claimed encompasses method of producing and using the above mentioned skin construct for transplantation or implantation into a patient.

Even though the specification teaches optimization of culture conditions for human fibroblasts to produce a layer of extracellular matrix in the absence of exogenous matrix components (see spec. Examples 1, 3 and 15), the specification fails to disclose what are the culturing conditions i.e. culture media contents, growth factors, culture environment that leads to the synthesis of (i) type I and type III collagen, (ii) decorin, (iii) fibronectin, (iv) tenascin, and, (v) glycosaminoglycans. Specifically, the specification fails to disclose a culturing condition (culture media contents, growth factors, culture environment) in which the fibroblast cells when cultured fibroblasts produce type I and type III collagens (as claimed) and tenascin. The specification fails to identify type I and type III collagens (as claimed) and tenascin in the extracellular matrix secreted by cultured fibroblasts. In addition the specification fails to disclose that fibroblast cells derived form tissues selected from form tendon, lung, cartilage, urethra, corneal stroma, oral mucosa, umbilical cord, and intestine are capable of synthesizing extracellular components (as claimed) under any and all culture conditions. Regarding formation of an epidermal layer the specification only disclosed the use of a specific culture conditions, which comprises culturing the seeded keratinocytes in an epidermalization medium followed by culturing of the skin construct under submerged conditions (air-liquid interface) in a culture media that is different from the epidermalization medium (Spec. page 46, example-16). The specification fails to disclose that use of any and all culture conditions (i.e. culture media contents, growth factors, culture environment) would lead to the formation of an epidermal layer (as claimed) in a cultured skin construct.

State of Art and Predictability

The state of the tissue engineering art at the time of filing teaches that to engineer living tissues in vitro, cultured cells are coaxed to grow on bioactive degradable scaffolds that provide the physical and chemical cues to guide their differentiation and assembly into three-dimensional tissues. The assembly of cells into

tissues is a highly orchestrated set of events that requires time scales ranging from seconds to weeks and dimensions ranging from 0.0001 to 10 cm. Coaxing cells to form tissues in a reliable manner is the quintessential engineering design problem that must be accomplished under the classical engineering constraints of reliability. Even though fewer than five engineered tissues have been approved, there are still many technical challenges to overcome before an "off-the-shelf" tissue could be created that represent the translation of scientific discoveries into treatments for patients. Furthermore, the successful large-scale production of engineered tissues requires an adequate source of healthy expandable cells, the optimization of scaffolds, and the creation of bioreactors, which mimic the environment of the body and that are amenable to scale-up. Additional challenges include the preservation of the product so that it has a long shelf-life and the successful use of various approaches to prevent tissue rejection (Naughton et al Science 295:1009-1014, 2002, ref of record).

Like in vivo conditions, hormones and growth factors were known to play a role for cell growth and ECM synthesis in vitro cell culture systems. Dermal fibroblasts in vitro were reported to proliferate and synthesize ECM in response to several hormones or growth factors. Compared to routine monolayer cultures, dermal fibroblasts in postconfluent cultures were shown to process more efficiently ECM components such as collagen. It has been found that post confluent dermal fibroblasts alone in a special culture condition could form several layers of cells in a culture dish. These findings and the problems of the previous dermal equivalents clearly prompts one skill in the art to to develop a safer and more practical alternative dermal equivalent (see Lee DY et al J Dermatol Sci. 43(2):95-104, 2006, Lee et al, Arch Dermatol Res. 296(7):296-302, 2005).

The state of the art teaches that specialized culture conditions are required for the formation of artificial skin constructs. For example the culture medium for the production of the new dermal equivalent was based on serum containing medium for the routine fibroblast monolayer culture that included EGF, insulin, hydrocortisone, transferrin and triiodothyronine. These supplements are all present and essential in the human body and they are known to support the growth of fibroblasts in vitro and EGF stimulates the growth and synthesis of non-collagenous proteins in cultured skin

fibroblasts, and its effect on collagen synthesis depends on the culture conditions . Insulin stimulates growth and collagen formation in cultured fibroblasts. Hydrocortisone increases growth as well as collagen and noncollagen protein production in cultured skin fibroblasts. Transferrin and triiodothyronine were included in some culture medium for culturing fibroblasts. Transferrin stimulates cell proliferation and proteoglycan accumulation of human fibroblasts. Triiodothyronine stimulates the synthesis of proteoglycan in human skin fibroblasts, but decreases the amount of newly synthesized collagen. In addition, serum, which is one of the most important factors that affect the growth and synthetic activities of cells, stimulates collagen production by fibroblasts. Thus, several supplements and serum may work together to influence cell growth and ECM synthesis of dermal fibroblasts, resulting in the formation of the fibrous matrix but the combination of nay such conditions would require further extensive and undue amount of experimentation. For example when postconfluent dermal fibroblasts were supplemented with ascorbic acid in a long-term culture a dermis-like matrix was produced. This result can be explained by the finding that ascorbic acid stimulates collagen production in cultured human skin fibroblasts. However, ascorbic acid has a disadvantage in that it is very unstable in solution, especially under the culture conditions of neutral pH and 37 °C. It was also reported that the addition of L-ascorbic acid 2-phosphate rendered fibroblasts to the organization of the dermis-like three-dimensional structure in vitro without any pre-treatments with the plastic dish. It was found that the dermis-like three-dimensional structure by addition of L-ascorbic acid 2-phosphate was much less formed compared to Lee et al products (see Lee DY et al J Dermatol Sci. 43(2):95-104, 2006).

Furhtermore the development of the basement membrane (BM) formation is complex and is controlled by various factors that include culture conditions and culture media content. For example type VII and type IV collagen are produced both by keratinocytes and fibroblasts and recent studies indictes that next to the use of serum-free medium, the number and the functional state of fibroblasts incorporated into the matrix also strongly affects the normalization of the epidermal differentiation program. The information on the role fibroblasts play in regulation of synthesis and deposition of

proteins at the dermalepidermal junction (DEJ) is limited. Previous studies mainly used fibroblast-populated dermal matrices or media supplemented with growth factors and studies with organotypic keratinocyte monocultures are scarce. The majority of the studies performed until now used media supplemented with growth factors, the effects of exogenously added growth factors were examined as well. I thas been indicated that that plectin, BP230, BP180, and integrins $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_3\beta_1$, and $\alpha_6\beta_4$ are constitutively produced by keratinocytes, and most importantly that fibroblasts or exogenously added growth factors plays an important role for deposition of the BM proteins laminin 5, laminin 10/11, Ladinin-1, uncein, and type IV and type VII collagen. In conclusion, the findings clearly demonstrated that a dermal equivalent, that closely resembles a dermis in vivo, could be constructed by culturing dermal fibroblasts alone in a special culture medium (see Ghalbzouri et al, J Invest Dermatol. 124(1):79-86, 2005).

Furthermore many studies identified the role of various growth factors in cutaneous physiology in order to add cytokines in a timely fashion for optimal tissue engineering of skin. The development process requires a multistep approach for the production of bioengineered skin substitutes, taking into account the effects of various growth factors according to the culture time. The state of the art clearly emphasize the need for sequential addition of the exogenous factors to the medium used to produce skin substitutes, in order to achieve required structural features and functional properties in-vitro (see. Auquer at al, In Vitro Cell Dev Biol Anim. 36(2):96-103, 2000)

Therefore as evidenced above the state of the art clearly teaches that the identification of the "culture conditions" along with the "contents of chemically defined culture media" are the most important aspects required for the development of an artificial skin construct of a clinical relevance, which would enable one skilled in the art to practice the invention as calimed without further undue amount of experimentation.

Under the law Limitations appearing in the specification but not recited in the claim are not read into the claim. In re Prater, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-551 (CCPA 1969). See also In re Zletz, 893 F.2d 319, 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989). Furthermore, claims are interpreted in light of the specification does not mean that everything in the specification must be read into the claims.

Raytheon Co. v. Roper Corp., 724 F.2d 951, 957, 220 USPQ 592, 597 (Fed. Cir. 1983), cert. denied, 469 U.S. 835 (1984). See also MPEP § 2111 - § 2111.01. In instant case the invention as claimed encompasses multi-layered cultured skin construct comprising a layer of cultured dermal fibroblast cells which produce a layer of extracellular matrix in the absence of exogenous matrix components during any and all culturing conditions. The instant claims fail to recite what are the culturing conditions for example culture media contents, growth factors, culture environment that leads to the synthesis of the claimed extracellular matrix components (I and type III collagens, decorin, fibronectin, tenascin and any and all glycosaminoglycans to support the growth and proliferation of second layer of epithelial cells. Similarly the instant claims fail to recite what are the culturing conditions (culture media contents, growth factors, culture environment that leads to the formation of epidermis during any and all culturing conditions.

Furthermore, It is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (*See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966), Stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."*) Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.

Therefore defining culture conditions which are not limited to culture media alone but encompasses chemically defined medium and structures required for each step involved in the development of cultured skin construct which are considered essential practice the instant invention without further undue experimentation. Even though the specification discloses various chemically defined medias like growth medium, production medium, epidermalization medium, cornification medium, maintenance medium, chemically defined medium, seed medium, and other medias it is unclear which media is used at each step during the development of the cultured skin construct

as claimed. Similarly the disclosure of a structure in the absence of a mesh member is considered essential practice the instant invention without further undue experimentation.

Under the law, the disclosure "shall inform how to use, not how to find out how to use for themselves." See In re Gardner 475 F.2d 1389, 177 USPQ 396 (CCPA 1973). At issue, under the enablement requirement of 35 U.S.C. 1 12, first paragraph is whether, given the Wands factors, the experimentation was undue or unreasonable under the circumstances. "Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See Fields v. Conover, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970). In instant case the with the identification of culture conditions eve one skill in the art would have to engage in excessive and undue experimentation to practice the invention as claimed.

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of skill.

In instant case making a multi-layered cultured skin construct under any and all culture conditions (culture media contents, growth factors, culture environment etc) is not considered routine in the art and without sufficient guidance to a specific "culturing conditions" the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Response to Arguments (enablement)

The applicant argues that to overcome the current rejection and to address the state of the art and predictability arguments raised in the last office action the applicant has filed the *Third Declaration Of Katherine C. Faria ("Third Faria Declaration")*. The applicant sites that "Third Faria Declaration, para. X" explains why the invention as claimed is not considered unpredictable. However the applicant's arguments are found not persuasive because applicant fails to file any *Third Declaration Of Katherine C.*

Faria ("Third Faria Declaration"). Therefore the rejection is maintained for the reasons of record as set forth in the earlier office action. As stated earlier the scope of "culturing conditions" as claimed is not limited to the disclosure of culture media alone but encompasses conditions under which a designated media(s) is used to make the cultured skin construct as claimed. The invention as claimed encompasses multi-layered cultured skin construct comprising a layer of cultured dermal fibroblast cells, which produce a layer of extracellular matrix in the absence of exogenous matrix components during any and all culturing conditions. As stated earlier the invention as claimed fails to recite what are the culturing conditions, for example, culture media contents, growth factors, support structure and culture environment etc that leads to the synthesis of the claimed extracellular matrix components (I and type III collagens, decorin, fibronectin, tenascin and any and all glycosaminoglycans to support the growth and proliferation of second layer of epithelial cells. Similarly the instant claims fail to recite what are the culturing conditions *(culture media contents, growth factors, culture environment that leads to the formation of epidermis)*.

Although a claim should be interpreted in light of the specification disclosure, it is generally considered improper to read limitations contained in the specification into the claims. See In re Prater, 415 F.2d 1393, 162 USPQ 541 (CCPA 1969) and In re Winkhaus, 527 F.2d 637, 188 USPQ 129 (CCPA 1975), In re Van Guens, 988 F.2d 1181, 26 PSPG2d 1057 (Ded. Cir. 1991), which discuss the premise that one cannot rely on the specification to impart limitations to the claim that are not recited in the claim.

Accordingly, without the recitation of all these critical limitations, the claims do not adequately define the instant invention. Similarly in the instant case the claims fail to recite what encompasses the "chemically defined media" or "culturing conditions" as claimed. In addition it would require an extensive and undue amount of experimentation to practice the invention as claimed especially in view of the state of the art that clearly teaches the role of various growth factors a culture for the development of an artificial skin construct that is of any practical use.

Conclusion

No claims are allowed.

This is an RCE of applicant's earlier Application No. 09523809. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SUMESH KAUSHAL
PRIMARY EXAMINER